ARNOLD & PORTER
555 TWELFTH STREET, N.W.
WASHINGTON, D.C. 20004-1202
(202) 942-5000
FACSIMILE (202) 942-5999

NEW YORK
DENVER
LOS ANGELES
LONDON

DONALD O. BEERS
(202) 942-5012

September 23, 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 10-61
Rockville, Maryland 20857

Re: Docket No. 99P-1589; Response of Roxane Laboratories to August 20, 1999 Submission by Purdue Pharma L.P.

Dear Sir or Madam:

On behalf of Roxane Laboratories, Inc. ("Roxane"), we submit this response to the August 20, 1999 Purdue Pharma L.P. ("Purdue") submission to the docket.

The Purdue submission accuses Roxane of mischaracterizing Purdue's positions. Certainly the Purdue filing mischaracterizes Roxane's position. In this response, Roxane will attempt to clarify what it understands the issues to be, based on a good faith attempt to understand Purdue's arguments.

Several points remain to be made:

ROXANE HAS NOT MADE "CONCESSIONS"

The notion in the Purdue filing that Roxane has implicitly conceded any point made by Purdue should be ignored. Any concessions that Roxane makes will be made explicitly and without ambiguity.

PURDUE SEEMS TO BE ARGUING FOR RELIEF NOT SOUGHT IN ITS PETITION

At several points, Purdue now seems to have changed the focus of its argument. It now seems to be asking that FDA reverse its findings that 1) the Roxicodone SR™ clinical studies are adequate to establish efficacy, 2) no pharm-tox studies are necessary to establish the safety of this long-marketed active ingredient, and 3) the approved labeling of Roxicodone SR is truthful and not misleading. If Purdue is now asking FDA to commence proceedings to withdraw approval of the Roxicodone SR NDA on one or

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more of these grounds, it should amend its petition to ask for that relief. Roxane is confident that FDA would reject any such request.

THE ROXANE PIVOTAL CLINICAL TRIALS ESTABLISHED THE EFFECTIVENESS OF ROXICODONE SR

Purdue claims that the pivotal clinical trials conducted by Roxane failed to establish statistically valid evidence of equivalent effectiveness for the Roxicodone SR product when compared to immediate release oxycodone. This assertion is based on a selective reading of language from the review of the Roxicodone SR studies by the FDA's statistical reviewer. While the reviewer discussed technical points about the difficulty of determining "equivalence" as a matter of statistics, the reviewer stated:

> It seems reasonable to conclude that the SR formulation was indeed effective for the proposed indication, otherwise it would be hard to believe that a placebo could have produced such similar efficacy profiles on patients with chronic moderate-to-severe cancer or non-cancer pain.

Statistical Review and Evaluation, 28 October 1998 at 20. The reviewer went on to state:

> Overall, it seems reasonable to believe that the SR and IR formulations were similar in the efficacy end points measured in these two trials.

Id. at 21. Accordingly, the reviewer recommended approval of the sustained release formulation of oxycodone for its proposed indication. Id. at 22.

The FDA, of course, concluded that the SR formulation was in fact proven effective for its proposed uses in studies in which the control group had received the IR formulation.

Certainly, there is nothing in any FDA document, or in the Roxicodone SR NDA, that supports in any way Purdue's suggestion that the NDA, and FDA, relied upon the Purdue clinical trials of OxyContin instead of Roxane's own trials of Roxicodone SR as proof of the effectiveness of Roxicodone SR. Accordingly, Purdue's allegations with respect to the effectiveness issue provide no support for its petition's request that FDA reclassify this application as a Section 505(b)(2) application. If Purdue is instead now arguing that FDA should reverse itself, find Roxane's studies to be inadequate, and commence proceedings to withdraw approval of the Roxicodone SR NDA on that basis, there is no basis for that relief either.

USE OF AN ACTIVE CONTROL GROUP DOES NOT MAKE THE ROXICODONE SR NDA A SECTION 505(b)(2) APPLICATION

The initial Purdue petition seemed to argue that the fact that the pivotal clinical trials in the Roxicodone SR NDA used the immediate release formulation of oxycodone as an active control was a basis for finding the application to be a Section 505(b)(2) application in the absence of a right of reference to every study showing the effectiveness of the immediate release formulation. As discussed in Roxane's prior submissions, such a position would be untenable as it would have the effect of making almost all NDAs for drugs for which active controls must be utilized into 505(b)(2) applications.[1] Purdue now seems to have clarified its argument no longer to assert that the use of an active control makes an application a 505(b)(2) application in the absence of a right of reference to data supporting the active control.

THE ROXICODONE SR NDA DID NOT RELY ON PURDUE TERATOLOGY AND TOXICOLOGY STUDIES

As noted, Purdue seems to have strayed from the relief it requested in its petition – i.e., that the Roxicodone SR NDA be "recognized" as a Section 505(b)(2) application. Instead, it now argues that the approval of this application as a Section 505(b)(1) application must be withdrawn by FDA because FDA did not require Roxane to complete certain short-term toxicity studies that Purdue says were required with respect to OxyContin. Alternatively, Purdue seems to argue that the approval should be withdrawn because the references in the Roxicodone SR draft labeling to data relevant to pregnancy are, according to Purdue, false or misleading.

Competitors are often in the position of second-guessing FDA approval decisions of competitor's products. Presumably, Roxane could, by studying the OxyContin NDA, find a basis to disagree with various FDA decisions that led to approval of that product. The exercise is not, however, productive. FDA has ample authority and discretion to

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[1] Purdue's August 20 submission contains extensive citation to a book, Beers, Generic and Innovator Drugs: A Guide to FDA Approval Requirements, authored by Roxane counsel. Despite Purdue's suggestion to the contrary, the references all appear to be consistent with Roxane positions. Even if they were not, Roxane would of course not be bound by them. It should be noted, however, that the suggestion by Purdue that a statement in the book contradicts Roxane's argument that it need not have a "right of reference" to effectiveness data on immediate release oxycodone (Purdue August 20 submission at 3 n. 3) is incorrect. While it appears to be FDA's position that a right of reference is necessary for a published report of a study relied upon for approval in order to avoid 505(b)(2) NDA status, that does not mean that there must be such a right of reference to a published report upon which the NDA does not rely for approval.

make judgments as to what will be required in the approval of an NDA and has done so here.

ROXANE DID NOT RELY ON STUDIES AS TO WHICH IT DOES NOT HAVE A RIGHT OF REFERENCE IN THE ROXICODONE SR NDA

Roxane is unclear as to why Purdue is arguing about whether the term "rely" encompasses the concept of "intent". It is worth mentioning, however, that a common dictionary meaning of the term "rely" does encompass the concept that reliance is voluntary. See, e.g., Webster's New World Dictionary (Second College Ed. 1984), defining "rely" as relevant here as "to look to for support or aid, depend." at 1201. The statutory question is upon what did the applicant rely, so presumably the applicant has some choice in the matter. Here, the NDA itself is very clear that the applicant relied upon the studies that it itself performed to satisfy the submission requirements of Section 505(b)(1)(A), i.e., in FDA's term, the investigations "without which the application could not be approved."

Certainly there is no requirement that, to avoid Section 505(b)(2) status, an NDA contain an explicit statement declining to rely upon studies that are included in the application only because of the FDA regulation's requirement of full disclosure of relevant data.[2]

ROXANE'S SUBMISSION OF PATENT INFORMATION WAS ACCURATE

The "Patent Information" section of an NDA is required by FFDCA Section 505(b)(1) and 21 C.F.R. §314.50(h) and 314.53 and requires the submission of information on patents "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug," Section 505(b)(1). Unlike the "Patent Certification" requirement applicable to Section 505(b)(2) NDAs and to ANDAs--see 21 C.F.R.§314.50(i)(1)(i) and 314.94(a)(12)--there is no requirement under the "Patent Information" provisions that reference be made to patents simply because they are listed in the Orange Book, when claims cannot reasonably be asserted under those patents for the drug in question.

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[2] The quotation from the Beers book does not say otherwise. Certainly, counsel for Roxane can state with confidence that the author of that text did not intend to say otherwise.

The "Patent Information" section of the Roxicodone SR NDA correctly stated that there are no patents that claim this product with respect to which a claim of patent infringement could reasonably be asserted. Purdue may disagree with that statement, and in fact the parties are likely ultimately to litigate this issue (assuming Purdue sues Roxane in a proper jurisdiction). Certainly, it is highly inappropriate for Purdue to ask FDA – which has no patent expertise – to resolve this issue of patent coverage in the context of this Petition.

ONLY INVESTIGATIONS SUBMITTED PURSUANT TO SECTION 505(B)(1)(A) ARE RELEVANT TO SECTION 505(B)(2) STATUS

Purdue clarifies that it is not arguing that the listing of studies to which the applicant does not have a right of reference in a Section 505(b)(1) NDA converts that NDA into a Section 505(b)(2) NDA. (August 20, 1999 submission at 6.) Purdue nevertheless appears to continue to claim that any labeling statement that could be said to refer to a study for which the applicant does not have a right of reference converts the NDA into a Section 505(b)(2) NDA. Purdue's position on this point is inconsistent with the statute. As Roxane has previously argued, the only relevant question for purposes of determining Section 505(b)(2) status is whether "the investigations described in clause (A) of" Federal Food, Drug, and Cosmetic Act Section 505(b)(1) are ones as to which the applicant has a right of reference. Not all information in an NDA is an investigation described in Section 505(b)(1)(A). No right of reference to information that is instead submitted in support of the requirements that the labeling of a drug should be truthful and informative--see Sections 505(b)(1)(F) and (d)(7)—is required to avoid Section 505(b)(2) status.

In its detailed defense of its theory that the Roxicodone SR application is a 505(b)(2) application based on references to data that informed the labeling of the product but were not the basis of approval, Purdue fails totally to address the flaw in its statutory argument. As noted, it is simply not the case that any information referred to in the labeling of a drug is a pivotal "investigation[] described in clause (A) of" Section 505(b)(1).

Purdue states that "the concept of 'class labeling' has no place in the approval of a product that is seeking to avoid § 505(b)(2) status by relying solely on its own data," (August 20, 1999 submission at 15). If Purdue's theories were to be accepted, class labeling would have to be abolished in most cases, even where totally new chemical entities were involved. Thus, for example, any NDA for a new NSAID would become a Section 505(b)(2) NDA, subject to the market exclusivity and patent provisions, if (as is always the case) its labeling referred to information about the use of other NSAIDs. That

is clearly wrong. Where relevant information is available from other products in a class, it is generally included in the labeling in order to make that labeling truthful and informative, and no one (except apparently Purdue) argues that doing so makes the application a Section 505(b)(2) NDA. See, e.g., 21 C.F.R. §201.57(g)(1).

To the extent that Purdue has in fact changed its tack entirely and is now arguing that the approval of the NDA should be withdrawn because of what it asserts is false or misleading labeling, Roxane of course disputes that characterization of the labeling. Because Purdue's petition does not ask for relief based on that assertion, Roxane will not respond to those assertions on a point-by-point basis. As noted above, the failure to address some argument made by Purdue counsel should not be, in any sense, considered a concession or agreement with respect to that issue.

THE APPROVAL OF THE ROXICODONE SR NDA WAS APPROPRIATE AND VALID; ROXANE WILL INSIST ON THE PROCEDURAL PROTECTIONS GRANTED TO IT BY THE STATUTE SHOULD FDA ACCEPT ANY PURDUE ARGUMENT

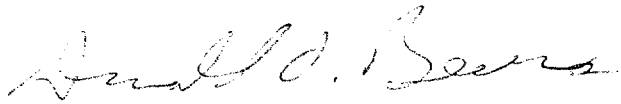
As noted in Roxane's prior filing, the Federal Food, Drug, and Cosmetic Act does not give the FDA the option simply to decide, as Purdue urges, that it made a mistake in approving an NDA and to withdraw that approval summarily. Instead, appropriately, the statute provides that withdrawal of approval can be based only upon the issuance of a notice of opportunity for a hearing. Where, as here, factual issues are involved, a full hearing is then required on the asserted basis for withdrawal. Roxane is confident that FDA's approval of this application as a Section 505(b)(1) application was correct and fully intends to assert its procedural rights to defend that approval should FDA accept – as it should not – any of the various theories Purdue has put forth in an unjustified attempt to protect itself from competition.

CONCLUSION

The Roxicodone SR NDA was clearly submitted as a Section 505(b)(1) new drug application. It relied for approval on the studies that Roxane itself performed on its drug. While Purdue's fears of the economic consequences of competition have driven it to urge FDA to make radical changes in FDA's processing of new drug applications – changes

that would have significant effects on the FDA approval process generally – there is no basis for making those changes. The petitions submitted by Purdue should be, in all respects, denied.

Respectfully submitted,



Donald O. Beers
David E. Korn
ARNOLD & PORTER
555 Twelfth Street, N.W.
Washington, D.C. 20004
(202) 942-5000